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(54) Pharmaceutical compositions comprising catecholic butanes.

(57) The invention relates to pharmaceutical compositions useful in the treatment of benign, premalignant and malignant solid tumours, especially those of the skin, and in the treatment of other disorders of the skin e.g. psoriasis and acne. The compositions comprise at least one catecholic butane. The preferred catecholic butane is nordihydroguaiaretic acid. The compositions are preferably applied topically or by intratumor or subcutaneous injection. The invention also includes sunscreening agents comprising at least one catecholic butane.

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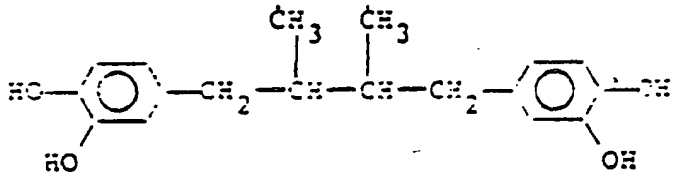
PHARMACEUTICAL COMPOSITIONS COMPRISING CATECHOLIC BUTANES

This invention relates to new methods of treating benign, premalignant and malignant solid tumours, particularly those of the skin, comprising the application to said solid tumors of the herein defined catecholic butanes and pharmaceutical formulations containing said catecholic butanes. The methods according to the invention are also effective in preventing the occurrence of benign, premalignant and malignant solid tumors of the skin when applied prophylactically to subjects exposed to a high risk of cancer causing agents, for sensitization of tumors to X-ray radiation and for the treatment of liver cancer. The methods according to the invention are also useful in the treatment of diseases and disorders of the skin such as acne and psoriasis, in aiding the healing of skin wounds and breaks in the skin and for antiviral, antibacterial and antifungal uses.

Methods of treating premalignant and malignant growths of the skin have often been traumatic. A common method of treating disorders such as actinic keratosis has been the application of liquid nitrogen to destroy the affected tissue. Epidermal tumors are commonly treated by physical removal through surgery. A method which has been used in the past is chemosurgery through the application of escharotic or fixative chemicals such as zinc chloride. This method has not been found to be particularly effective because of the physical discomfort associated with the use of such materials. It also has the disadvantage of destroying both healthy tissue and the diseased tissue. Neither has the use of known antitumor drugs been found to be particularly effective in the treatment of skin tumors since these drugs are commonly applied systemically resulting in substantial side effects due to their toxicity.

The naturally occurring meso form of the catecholic butane, nordihydroguaiaretic acid [meso-1,4-dihydroxyphenyl)-2,3-dimethylbutane] ("NDGE") is found in the creosote bush, and its general structure (generic to all of its stereoisomeric forms) is given in Formula (I).



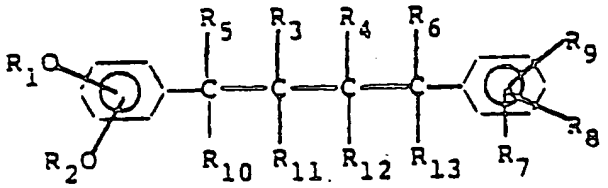
The creosote bush was used for centuries to brew a tea which was the basis for a folk remedy that called for drinking the tea to cure colds, rheumatism and other ailments. However, this remedy has not proven to be successful. NDGA was also used for years as an antioxidant to inhibit the development of rancidity in the fats of food products and as a stabilizer of pharmaceutical preparations, perfumary oils, rubber and other industrial products.

C.R. Smart et al. in the Rocky Mountain Medical Journal, Nov. 1970, pp. 39-43, conducted clinical studies to ascertain the validity of an earlier report of tumor regression in a melanoma of a patient taking "Chaparrel Tea", which contains NDGA. In the clinical study conducted by Smart et al., human cancer patients ingested either "Chapparrel Tea", an aqueous extract of Larrea divericata containing NDGA, or doses of pure NDGA. Although some positive results were observed, the authors advised against treatment with "Chaparrel Tea" due to a significant number of reported cases of tumor stimulation. This confirmed the earlier screening studies of NDGA conducted by Leiter et al. of the Cancer Chemotherapy National Service Center of the National Cancer Institute, which obtained negative results when NDGA was tested against several types of cancer cells.

Surprisingly, it has now been discovered that catecholic butanes, particularly nordihydroguaiaretic acid, and/or derivatives thereof as defined herein, in a pharmaceutical composition, are effective in treating benign, premalignant and malignant growths, preferably when directly applied to the situs, without the detrimental side effects associated with chemotherapy or chemosurgical techniques. The compositions provide particularly advantageous results when applied topically to the afflicted area of the skin, or injected into the growth.

are also effective in treating disorders of the skin including acne and psoriasis, in aiding in the healing of skin wounds and in alleviating bacterial, viral and fungal infections when applied to the situs of the disorder. The compositions are also useful in the treatment of warts.

This invention relates to methods useful in the treatment and prevention of benign, premalignant and malignant solid tumors, especially those of the skin, comprising the application of pharmaceutical formations having a catecholic butane of the formula:



(II)

wherein R_1 and R_2 are independently H, lower alkyl, lower acyl, or alkylene;

R_3, R_4, R_5, R_6, R_{10}, R_{11}, R_{12}, and R_{13} are independently H or lower alkyl;

R_7, R_8 and R_9 are independently H, hydroxy, lower alkoxy, lower acyloxy, or any two adjacent groups together may be alkylene dioxy.

Alkylene dioxy generally means methylene (or substituted methylene) dioxy or ethylene (or substituted ethylene) dioxy. Lower alkyl is intended to generally mean C_1-C_6 alkyl, and preferably R_3 and R_4 are C_1-C_3 alkyl. Lower acyl is intended to generally mean C_1-C_6 acyl, with C_2-C_6 acyl being preferred. It will be appreciated by those skilled in this art that Formula II is directed to both the phenolic compounds and the conventional esters and ethers thereof.

The invention comprises a method of inhibiting the abnormal growth of cells, such as malignant melanoma cells, human mammary tumor cells, and human lung squamous cell carcinoma cells by contacting the cell with pharmaceutical compositions adapted for topical, parenteral, subcutaneous, or intralesional administration comprising, in admixture with a pharmaceutically acceptable carrier, a catecholic butane of Formula (II). Thus, the invention comprises methods for inhibiting the abnormal growth or proliferation of cells in mammals which preferably comprise applying an amount of said catecholic butane effective to inhibit said abnormal growth directly to the situs of the abnormal growth of cells by topical application or by injection into the interior or near vicinity of the afflicted situs. The preferred compositions comprise nordihydroguaiaretic acid and such compositions in combination with pharmaceutically acceptable carriers.

In a further method of use, the invention comprises a method of preventing the growth of benign, premalignant and malignant cells by prophylactically applying said composition comprising catecholic butanes to a particular body site which may be abnormally exposed to a cancer inducing stimulus.

In a further embodiment, this invention comprises the application of a formulation comprising about 0.05 to about 20 weight percent of substantially pure cetecholic butane, NDGA in a preferred embodiment, in combination with a toxicologically acceptable carrier.

The term "afflicted situs or area" or similar language, as used herein, refers to a localized area of pathology, infection, wound, lesion, or abnormal cells, including tumors, and the surrounding area.

The term "applying" as used herein embraces both topical applications to a surface of the afflicted situs and injection into the interior of the situs.

The term "mammal" as used herein includes feline, canine, equine, bovine, rodent and primate species, including cats, dogs, horses, rats, mice, monkeys and humans. Other animals e.g., birds, can also be successfully treated with the compositions of this invention.

The term "abnormal growth of cells" refers to benign, premalignant and malignant cells. Examples of the former include the cells associated with adenomas, papillomas, etc. Examples of premalignant cells include actinic keratosis.

The term "escharotic" means a corrosive or caustic agent which is capable if killing healthy, living cells.

The term "solid tumor" refers to tumors in which a plurality of tumor cells are associated with one another, i.e. contiguous and localized within a confined site. This is to be contrasted with "fluid" or "hematogenous" tumors in which the tumor cells occur primarily as unassociated or individual cells, e.g. leukemia. Solid tumors generally propagate on host tissues such as the epithelial, the connective and supportive tissues as well as other tissues located throughout the body. Examples of epithelial tumors include papillomas such as verruca verruciformis and carcinomas such as squamous cell carcinoma, basal cell carcinoma, adenoma, adenocarcinoma, cystadenoma, cystadenocarcinoma and Bowenoid carcinoma. Examples of supportive and connective tissues tumors include sarcomas and their benign counterparts such as ribrosarcoma, fibroma, liposarcoma, lipoma, chondrosarcoma, chondroma, leiomysarcoma, and leimyoma. Examples of other tissue tumors include gliomas (brain tumors) and malignant melanomas.

The term "pharmaceutically-acceptable carrier" refers to a material that is non-toxic, generally inert and does not adversely affect the functionality of the active ingredients.

The methods according to the invention comprising the use of catecholic butanes are surprisingly effective in the treatment of a variety of solid tumors and skin disorders, and are particularly effective when

the afflicted areas, or the areas having an abnormal exposure to cancer including stimuli, are directly contacted with the instant compositions. The methods according to the invention have unexpectedly been found to provide improved restoration of integrity to injured tissue and cause the regression, elimination or prevention of solid tumors arising from all three embryonic tissue types, namely squamous cell carcinoma, e.g., lung carcinoma, arising from the ectodermal layer; adenocarcinomas, e.g. breast, renal and colon cancer, arising from the endodermal layer; and melanoma and brain cancers, arising from the mesodermal layer.

More specifically, the methods of the instant invention have been found to be effective against the following solid mammalian tumors: mouse Sarcoma-180; human tumors including malignant melanoma, Sarcoma-180, squamous cell carcinoma, lung squamous cell carcinoma, breast adenocarcinoma, glioma, glioastrocytoma, renal-cell carcinoma, colon, Bowenoid carcinoma and basal cell carcinoma; equine tumors including papillomas, malignant melanoma, sarcoid and squamous cell carcinoma; and canine tumors including squamous cell carcinoma, breast adenocarcinoma, perianal adenoma, basal cell carcinoma and mast cell tumor.

Thus, the pharmaceutical compositions of the present invention are useful for the prevention of the occurence of and/or the treatment of solid mammalian tumors selected from human malignant melanoma, human mammary tumor and human squamous lung cell carcinoma; equine sarcoid, equine paplilloma, equine malignant melanoma, equine squamous cell carcinoma; canine perianal adenoma, canine mast cell carcinoma, canine breast adenorcarcinoma and canine malignant melanoma.

The pharmaceutical compositions of the present invention are also useful for the prevention of the occurance of and/or the treatment of disorders of the skin such as actinic keratosis, acne, psoriasis, skin wounds, warts, bacterial infections, fungal infections and viral infections.

The composition may be applied, for example, in an amount of 10 nanomoles to each milliliter of solid tumor. The composition is conveniently applied by topical administration, subcutaneous injection or intratumor injection.

The novel methods of this invention are particularly useful in the treatment of keratoses, especially actinic keratosis and senile keratotic lesions, as well as certain cutaneous tumor manifestations of otherwise systemic diseases. The novel methods of the invention have also been found to be effective against equine diseases such as sarcoid, papilloma, malignant melanoma and squamous cell carcinoma, and against canine diseases such as perianal adenoma, mast cell carcinoma, breast adenocarcinoma and malignant melanoma.

The preferred catecholic butane according to the invention, NDGA, has been found to be particularly effective against the following solid human tumors: melanoma (B-16), lung squamous cell carcinoma (LX-1), and human breast adenocarcinoma (MX-1).

It has also been discovered that the catecholic butanes, particularly NDGA, when applied topically, enhance the X-ray radiation effectiveness of the tumor cells without radiation toxicity to surrounding uninvolved skin. Consequently, the catecholic butanes may be useful in the treatment of cutaneous afflictions such as Kaposi's sarcoma.

The invention has also been found to be effective not only in eliminating or ameliorating tumors, but in preventing their occurrence when applied prophylactrically. It has been observed that the catecholic butanes are effective in reducing the potential and preventing tumor promotion and the reducing the potential of tumor induction. Thus, the catecholic butanes, e.g., NDGA, are not only effective in preventing cancer formation after cancer induction, but also can be used to prevent cancer development in industrial workers exposed to a carcinogenic agent. In this regard, it is contemplated that the catecholic butanes may be applied prophylactically to a site having abnormal risk to carcinogenic agents or stimuli.

To prevent the establishment of cancer, the catecholic butanes can be formulated into creams and ointments or in cosmetic bases to be used daily, preferably topically. the catecholic butanes can also be used together with a sunscreen to prevent sunlight induction of cancer and sunlight promotion of existing cancers. Surprisingly, the catecholic butanes, particularly NDGA, have been shown to be effective sun-screening agents. In this regard, NDGA has been shown to strongly absorb sunlight at wavelengths known to produce sunburn. Thus, the catecholic butanes can be used to block sunlight and thereby prevent sunlight induction of cancer or promotion of existing cancers.

The method according to the instant invention are also useful in conjunction with surgery for removal of internal cancers to eradicate residual tumor cells and to act as a prophylactic against local recurrence and metastatic spread of the tumor. The instant compositions may be applied to the effected area in lieu of surgery when there are cosmetic considerations due to the normally improved appearance of the healed situs treated with the instant compositions compared to surgery alone.

The catecholic butanes useful in the methods of the instant invention, particularly NDGA, have also

been found to be effective in treating hepatic and colon carcinoma. The catecholic butanes, when applied parenterally or by injection, are excreted primarily through the liver and gut, and therefore exert preferential cytotoxicity to tumors located in those organs.

The catecholic butanes useful in the methods of the instant invention are of the Formula (II), and are commonly available from Aldrich Chemical Co., Milwaukee, Wisconsin or can be synthesized by known methods. Illustrative classes of compound within the scope of Formula (II) are those wherein:

a) one or more of R_1, R_2, R_3, R_4, R_5, R_6, R_7, R_8, R_9, R_{10}, R_{11}, R_{12} and R_{13} are H, e.g., those wherein R_5 is H, R_5 and R_6 are H or R_5, R_6 and R_7 are H and R_8 and R_9 are OH or OR_1;

b) R_3 and R_4 each are CH_3 or C_2H_5 including those wherein R_5, R_6 and R_7 are H and/or R_8 and R_9 are OH and OR_1;

c) R_1 and R_2 are lower acyl, e.g., hydrocarbonacyl, preferably, alkanoyl, e.g., acetyl, propionyl, etc., including those of a) and b);

d) R_1 and R_2 are alike and R_8 and R_9 are OR_1, including those of a), b) and c); and;

e) The compound is in the form of a single optical isomer or a mixture of such isomers, e.g., a racemic mixture, or diastereoisomers including each of a), b), c) and d).

As used herein, lower alkyl represents, inter alia, methyl, ethyl, n-propyl, isopropyl, n-butyl, iso-butyl, tert-butyl, n-pentyl, isopentyl, n-hexyl, and the like.

Lower acyl represents groups having the general formula RCO-, e.g., acetyl (CH_3CO-), propionyl (CH_3CH_2CO-), butyryl ($CH_3CH_2CH_2CO$-), and the like. When the catecholic butane compound is named as a substituted phenyl, the corresponding groups are acetoxy (CH_3CO_2-), propionyloxy ($CH_3CH_2CO_2$-), and butyroyloxy ($CH_3CH_2CH_2CO_2$-).

Examples of catecholic butanes include the d-, 1-, racemic mixture of d- and 1-, and meso-isomers of 1,4-bis(3,4-dihydroxyphenyl)-2,3-dimethylbutane; 1,4-bis (3,4- dihydroxyphenyl)butane; 1,4-bis (3,4-dimethoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-diethoxyphenyl)-2,3-dimethyl-butane; 1,4-bis(3,4-dipropoxyphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl)-4-(3′, 4′, 5′ -trihydroxyphenyl) butane; 1,4-bis(3,4-diacetoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipropionyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dibutyroyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-divaleroyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipivaloyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dineopentylcarboxylphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl)-4-phenylbutane and 1-(3,4-dihydroxyphenyl-4-(2,5 dihydroxyphenyl) butane. Mixtures of the Formula (II) catecholic butanes may be used in the instant compositions.

Nordihydroguaretic acid tetrapivalate and nordihydroguaretic acid tetrapropionate in any of their optical configurations may be employed in the present invention. The efficacious amount of catecholic butane used in the method of this invention may be varied over a wide range. The typical range of the amount of catecholic butane in the instant methods is between about 0.05 wt % and 20 wt % and preferably, the amount of catecholic butane applied according to the invention ranges between about 1 wt % and 10 wt %. As used herein, the weight percent in the formulations refers to the concentrations of materials being effectively delivered to the treatment site.

Generally, the efficacious amount and concentration of the catecholic butane to be applied are those which result in the composition exhibiting the property or properties required in the treatment for which the composition is being used, namely, anti-tumor activity. The preferred amounts depend upon the particular condition being treated, the method of delivery of the composition to the treatment site, e.g., topically or by injection, the rate of delivery of the active ingredients to the treatment site, and the number of applications of the formulation which can be used. Preferred amounts for any specification application may be determined by normal pharmacological screening methods used in the art. If desired, an excess of the catecholic butane can be used as appropriate for the specific condition being treated. It has been found that it is necessary to contact the tumor cells with at least a threshold amount of catecholic butane to observe an inhibition in growth of the neoplasm. This minimum amount has been found to be greater than about 10 nanomoles of catecholic butane per milliliter of tumor cells.

Generally, preferred amounts of the catecholic butanes with respect to two classes of tumors and exemplary application amounts/rate are shown in Table I.

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TABLE I

Treatment/Use	Preferred Amount of Catecholic Butane	Exemplary Application Amount/Rate of Catechol Composition
Pre-Malignant Tumors	0.05 to 15 wt.% of catecholic butane	Apply topically 100 mg/cm^2 to tumor. Repeat application when amount of prior application falls below about 1 mg/cm^2. Wound may be dressed until healing is complete. Healing period may extend for several months. Repeat daily
Solid Epithelial Tumors	0.1 to 20 wt.% of catecholic butane	as indicated by observation of tumor size reduction (i.e., if no reduction in size after 10 days, repeat 2-3 times daily; if reduction in size is observed, after 10 days, repeat at daily intervals or sooner if reduction in size ceases to continue). Healing period may extend for several months. Alternatively, 0.1 ml. of composition may be injected intralesionally at the tumor site.

The instant compositions can be applied topically to or injected into the treatment site, e.g., subcutaneously by injection. When used for topical applications, the catecholic butane is usually formulated with a pharmaceutically-acceptable carrier. The novel methods according to the invention have been found to be particularly effective when applied directly to the surface of the tumor or injected therein.

Carrier materials are well known in the pharmaceutical formulation art and include those materials referred to as diluents or vehicles. The carrier may include inorganic or organic materials and should have sufficient viscosity to allow spreading of the composition and provide good adherence to the tissue to which it is topically applied. Examples of such carriers include, without limitation, polyols such as glycerol, propylene glycol, polyethylene glycol, preferably of a molecular weight between about 400 and about 8000, suitable mixtures thereof, vegetable oils, and other materials well known to those skilled in this art. The viscosity of the formulation can be adjusted by methods well known in the art, for example, by the use of a higher molecular weight polyethylene glycol.

In addition to the catecholic butane and carrier, the formulation can contain pharmacologically-acceptable additives or adjuvants such as antimicrobial agents, e.g. methyl, ethyl, propyl, and butyl esters of para-hydroxybenzoic acid as well as chlorobutanol, phenol, ascorbic acid, etc. The formulation can also contain thickening or gelling agents, emulsifiers, wetting agents, coloring agents, buffers, stabilizers and preservatives including antioxidants such as butylhydroxyanisole in accordance with the practice of the art. The formulation can also contain penetration enhancers such as dimethyl sulfoxide, long-chain alcohols such as nonoxynol, long-chain carboxylic acids, propylene glycol, N-(2-hydroxyethyl)pyrrolidone, 1-dodecyl-azacycloheptan-2-one, and the like. Depending on the method of application and the disease being treated, it may be desirable to use absorption-delaying agents such as aluminum monostearate and gelatin.

The composition of the formulation can be adjusted using components well-known in the formulation art to provide a pharmaceutical formulation which is a gel, cream, ointment, solid, liquid, semi-solid, etc. The particular physical form of the formulation depends on the desired method of treatment and the patient to be treated.

Typical formulations of the pharmaceutical compositions of this invention are set forth in Table II.

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TABLE II

Application Form	Formulation	Grams
Ointment	Catecholic butane	(preferred amount: about 1-5 gr.)
	Peg 400	4.2
	Peg 8000	61.7
	Water	19.0
	Ascorbic acid	0.1
Gel	Catecholic butane	(preferred amount: about 0.1-2 gr.)
	Standard denatured alcohol	12.0
	Propylene glycol	22.5
	Water	53.4
	Non-ionic surfactant	6.0
	Xantham gum	4.0
	Ascorbic acid	0.1
Cream	Catecholic butane	(preferred amount: about 1-5 gr.)
	Ascorbic acid	0.1
	Benzyl alcohol	5.0
	Propylene glycol	23.0
	Water	35.4
	Stearyl alcohol	7.0
	Cetyl alcohol	4.5
	White petrolatum	13.0
	Poloxyl-40 stearate	7.0
Solid	Catecholic butane	(preferred amount: 1-10 gr.)
	Carnuba wax	8.9
	Beeswax	13.3
	Lanolin anhydrous	4.4
	Cetyl alcohol	4.4
	Ascorbic acid	0.1
	Castor oil	57.7
	Water	1.2
Injectible Liquid	Catecholic butane	(preferred range: 0.1-5 gr.)
	Water	31.9
	Glycerine	36.5
	Glycine	1.5
	Sodium ascorbate	0.1
	Propylene glycol	25.0

For administration by injection, the compositions according to the invention are formulated as solutions or suspensions having a low enough viscosity to be injected. The composition suitable for injectable use must be sterile and fluid to the extent that easy syringe injection exists. It should also be stable under conditions of manufacture and storage and be preserved against contamination by microorganisms. Preservatives include alcohol, benzoic acid, sorbic acid, and methyl and propyl paraben with and without propylene glycol. Additionally, the pH of the composition must be within a range which does not result in tissue damage, namely, between about 3-7.5.

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The concentrations of active ingredients in a particular formulation required to provide a particular effective dose may be determined by a person skilled in the pharmaceutical formulation art based upon the properties of a carrier and the particular additives introduced into the formulation. It is contemplated that formulations can be prepared that have significantly higher concentrations of catecholic butane depending upon the carrier and additives being used. If the carrier substantially retains the catecholic butane or releases it at a slow rate, the concentrations of the cetecholic butane in the formulation can be substantially increased and in fact may have to be substantially increased in order to provide an effective treatment. In practice, it is preferred that a formulation contain the lowest concentrations of catecholic butane which effectively treat the condition with the desired number of applications, i.e.,a lower effective dose rate can be tolerated if multiple applications are used. This low concentration limit is dependent upon the delivery effectiveness of the carrier vehicle. Preferably, the catecholic butane comprises between about 1 and about 10 weight percent of the formulation.

A preferred embodiment of the instant invention comprises compositions containing NDGA, i.e., meso 1,4-bis(3,4-dihydroxyphenyl)-2,3-dimethylbutane. This composition has been found to be particularly effective in treating solid tumors and actinic keratosis. Although the effective concentration of nordihydroguaiaretic acid delivered to the treatment site depends, inter alia, upon the carrier and other additives included in the formulation, ordinarily the concentration of NDGA in the formulation will range from about 1 to about 15 weight percent. These ranges are provided by way of description and not by way of limitation since it is recognized that the concentration may be adjusted over a wide range depending on the carrier material, number of applications used, etc., as described hereinabove.

The pH of the formulation is important in assuring stability of the catecholic butane as well as assuring that the formulation is physiologically acceptable to the patient. Many of the catechols, particularly nordihydroguaiaretic acid, are susceptible to oxidation, for example, by air. Such oxidation can result in discoloration of the formulation rendering it unacceptable for pharmaceutical use. These catechols are more stable against oxidation at lower pH levels. Therefore, it is preferred that if the formulation is to be exposed to oxidizing conditions the pH be maintained below about 7.5 and preferably below about 6 in order to provide maximum stability for the catechol against oxidation. However, if oxidizing conditions can be avoided, for example, by storage of the formulation under an inert atmosphere such as nitrogen, a higher pH can be used. The pH of the formulation may be maintained through the use of toxicologically-acceptable buffers. Such buffers are well known in the pharmaceutical formulation art, and include hydrochloric acid buffer, acid phthalate buffer, phosphate buffer and citric acid/sodium citrate buffer.

Alternately, antioxidants such as ascorbic acid, hydroxyquinone, sodium bisulfite, meta bisulfite, etc. can be added to the formulation.

In topical applications the instant compositions are applied to the affected area or afflicted situs of the patient. The term "topical" refers herein to the surface of the epidermal tissue, especially the skin, the surface of tumors on the skin which have been debrided or otherwise modified, as well as sites from which solid tumors have been removed either from the skin or internally.

In preparing a formulation suitable for topical application, the catecholic butane is normally mixed with a suitable solvent. Examples of solvents which are effective for this purpose include ethanol, acetone, acetic acid, aqueous alkaline solutions, dimethyl sulfoxide, glycerine, glycerol, propylene glycol, nonoxynol, ethyl ether, polyethylene glycol, etc.

Application by injection can be used for treatment of solid tumors in which removal by surgery is not desired or for which surgery is not medically advisable. In this procedure the instant composition is injected directly into the tumorous cells.

The methods of the instant invention have also been found to be useful in the treatment of lesions and draining wounds which show impaired healing. As used herein the term "lesion" refers to any pathological or traumatic discontinuity of tissue. A "wound" is a lesion which results from a bodily injury caused by physical means. Lesions which do not readily heal can be manifestations of conditions, diseases or infections, for example, cutaneous ulcers, osteomyletis, acne vulgaris, draining fistulas, etc. Not uncommonly, lesions do not heal properly and continue to drain which results in discomfort to the patient and a continued threat of severe infection. Such conditions in which tissue does not readily grow to heal the lesion or wound can be the result of bacterial infection or other causes not fully understood. Exposed areas created by the sloughing off of necrotic matter, generally result in pus formation (suppuration).

Direct contact of the exposed area of the wound or lesion with the instant compositions has been found in clinical studies to substantially aid the healing process, possibly by inducing the formation of granulation tissue. This promotion of healing has significant advantages, for example, in the treatment of solid tumors directly or the situs from which such tumors have been surgically removed in that healing is promoted concurrently with inhibiting the growth of any tumor cells which might remain at the site of surgery.

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In determining the efficacy of a catecholic butane formulation in the treatment of a tumor, initial screening is commonly done by the Human Tumor Clonogenic Assay (HTCA). It has been reported that clinical correlations form retrospective analysis and prospective clinical trials with such clonogenic assays have indicated that there is a 60 to 70% correlation between in vitro sensitivity and clinical response. The studies have also indicated that there is a greater than 90% correspondence between in vitro resistance and treatment failure. However, the screening of new antitumor agents is still primarily being conducted using a variety of tumor models in vivo. The National Cancer Institute is currently using in vivo tumor models which include the L-1210 lymphocytic leukemia, B-16, melanoma, S-180 Carcinoma, 3 transplantable murine tumors, and the MX-1 human mammary tumor xenograph.

The following examples are included by way of illustration and not by way of limitation. Unless otherwise indicated, the nordihydroguaiaretic acid used in the instant Examples was the meso-isomer and is designated NDGA. Other isomers are indicated, e.g., d,1-NDGA. While the mesoisomer is the most readily available, any of the isomers of nordihydroguaretic acid may be used in the present invention. In particular any of the racemic forms of nordihydroguaretic acid may be employed.

EXAMPLE I

The catecholic butane 1-(3,4-dihyroxyphenyl)-4-(2,3,4 -trihydroxyphenyl) butane was prepared by the following procedure.

500 grams of 3,4-dimethoxydihydrocinnamic acid was suspended in 1.6 liters of methanol containing 250 ml of 2,2-dimethoxypropane. To this mixture was added dropwise a solution made by adding 20 ml. of acetyl chloride to 400 ml of methanol. The resulting mixture was stirred overnight at room temperature and finally at reflux for one hour. The solvent was evaporated to give a syrup in quantitative yield, 533 g.

To 912 ml. of lithium aluminum hydride (1M in THF) was added dropwise 213 g. of 3,4-dimethoxydihydrocinnamic acid methyl ester dissolved in 900 ml of dry THF at such a rate as to maintain gentle reflux (5 hours). The reaction mixture was stirred overnight at room temperature, cooled in an ice bath and treated dropwise with ammonium chloride solution (saturated) (104 ml) over a two hour period. After stirring for several hours, the reaction mixture was diluted with 500 ml. of THF, filtered and the filtrate evaporated in a vacuum to give 160 g. (86%) of a light yellow oil.

3-(3,4-dimethoxyphenyl)propanol (202 g) was added to 218 ml of triethylamine in one and half liters of methylene chloride. This solution was cooled to -10 $^{\circ}$ C in an ice salt bath and 87.6 ml. of methanesulfonyl chloride was added dropwise over a one and a half hour period while stirring rapidly. Stirring was continued for another hour and the mixture was washed with 700 ml. of ice water, 700 ml. of 3N hydrochloric acid, 700 ml. of saturated sodium bicarbonate and finally with 700 ml. of brine. The organic phase was dried with sodium sulfate and evaporated in a vacuum to give an orange oil in quantitative yield, 282 g.

3-(3,4-dimethoxyphenyl)propanol methanesulfonate, 282 g., (1.029 mol.); KBr, 282 g. (2.37 mol.) and dicyclohexano-18-crown-6, 19.2 g. (0.01515 mol.) were stirred in refluxing acetonitrile, 2.8 liters (dried over 3A molecular sieves) for 22 hours. The mixture was filtered and the filtrate evaporated in a vacuum to give an orange oil, 267 g. The product could be purified by vacuum distillation at 0.5 mm Hg, b.p. = 113-116 $^{\circ}$ C.

3-(3,4-Dimethoxyphenyl)propyl bromide, 25.9 g., in 50 ml. of dry tetrahydrofuran (dried by distillation from LAH) was placed in a dropping funnel. Magnesium powder, 2.5 g., and a trace of iodine was placed in a dry three neck flask with nitrogen inlet and reflux condenser. The reaction started upon addition of the liquid reactant and reflux was continued over a three hour period during which time the metal dissolved in the stirred solution. The reaction was cooled and the volume made up to 200 ml. to form a 0.5M solution in dry THF.

2,3,4-Trimethoxybenzaldehyde, 1.96 g. (0.01 mole),. dissolved in 20 ml. of dry THF and 20 ml. of the 0.5M Grignard reagent from 3-(3,4-dimethyoxyphenyl)propyl bromide in THF was added dropwise at ice temperature. The mixture sat over night at room temperature. The solution was evaporated in a vacuum and 20 ml. of ethanol was added carefully followed by excess sodium borohydride. Refluxing for a few minutes destroyed the yellow color of the small amounts of ketone and other unsaturated impurities formed from oxidation of the product. Most of the ethanol was evaporated and the residue partitioned between water and ether, 50 ml. of each. The ether phase was dried over sodium sulfate and evaporated to give 4.65 g. of a pale yellow oil.

The 4-(3,4-dimethoxyphenyl)-1-(2,3,4-trimethoxyphenyl)butanol, 3.65 g., was treated with excess sodium hydride, 1 g., and methyl iodide, one ml, in 25 ml. of dry dimethylformamide during one hour of stirring. Water was added carefully dropwise at first and finally 500 ml. of water was added. The product was

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extracted three times with 50 ml. of chloroform and the solvent evaporated to give a colorless crude oily product that can be used in the next step without further purification.

About 100 ml of anhydrous ammonia was condensed into a three necked flask with a dry ice condenser and dry ice bath. The flask was protected from moisture with a soda-lime tube and flow of dry nitrogen. One gram of clean sodium metal was dissolved in the liquid ammonia and the whole of the crude product in 20 ml of dry tetrahydrofuran was added as quickly as possible. The dark blue solution was stirred rapidly for twelve minutes before enough methanol was added to destroy the blue color. Evaporation of the solvent under a vacuum gave a thick residue to which 500 ml. of water was added. The water solution was extracted twice with 50 ml. of chloroform that left three grams of oily residue on evaporation. Chromatography of this crude product on 300 g. of silica-gel using chloroform as an eluate gave 2.3 of pure 1-(3,4-dimethoxyphenyl)-4-(2,3,4-trimethoxyphenyl) butane (one spot on FLC).

A 1.15 g. sample of 1-(3,4-dimethoxyphenyl)-4-(2,3, 4-trimethoxyphenyl) butane was refluxed for nine hours in 50 ml. of 48% hydrobromic acid under an inert nitrogen atmosphere. Standing over the weekend allowed 641 mg. of tan product to settle out in the freezer. This material was recrystallized under inert atmosphere from methanol-water 1:20 to give light pink crystals, m.p. = 165-167° C.

The following compounds were prepared by a similar procedure:

a) 1-(3,4-Dihydroxyphenyl)-4-(3,4,5-trihydroxyphenyl)butane;
b) 1-(3,4-Dihydroxyphenyl)-4-phenylbutane
c) 1-(3,4-Dihydroxyphenyl-4-(2,5-dihydroxyphenyl) butane;
d) 1,4-Di(3,4-dihydroxyphenyl)-1,2,3,4-tetramethylbutane
e) 1,4-Di(3,4-dihydroxyphenyl)-2-methyl-3-ethylbutane
f) 1,4-Di(3,4-dihydroxyphenyl)-1-propyl-2-methyl-3-ethylbutane.

Example 2

NDGA was evaluated for its effect on human mammary carcinoma MX-1 xenograft in athymic nude NCr mice.

A 14 mg. fragment of the human mammary carcinoma MX-1 was planted subcutaneously into the axillary region of mice with a puncture in the inguinal region at day 0. Mice with tumours weighing no less than 75 mg. and no more than 350 mg. were selected and pooled on day 1.

Tumored groups of mice were injected with a 0.1 ml. volume of the appropriate test or vehicle control substance on day 1 only. Individual body weights were recorded on day 1 and two times per week thereafter until day 60, and individual tumors were measured with calipers on day 1, and twice per week thereafter through day 60. Mean tumor weights were calculated for each measurement day. Each day, change in mean tumor weight was determined for both the test and control.

0.1 ml. of Compositions A through I were injected intratumorally on day 1 with NDGA as set forth in the table below:

Composition	No. Mice	% NDGA in Composition
A	6	1.53 ± 0.06
B	6	2.49 ± 0.08
C	6	3.41 ± 0.18
D	6	4.61 ± 0.34
E	6	6.36 ± 0.69
F	6	7.62 ± 0.17
G	6	9.44 ± 0.16
H	6	15.40 ± 0.40
I	6	18.40 ± 0.30

The relative size (T/C%) of the tumor in the treated versus untreated animals was calculated as follows:

$$\frac{T}{C}\% = \frac{\text{wt. of tumor in treated animal}}{\text{wt. of tumor in untreated animal}} \times 100\%$$

Efficacy is indicated by T/C of less than 100%; the smaller the value, the more effective the

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composition as an antitumor agent.

The activity and duration of action of composition I is shown below:

Day	Animals Died	Relative Tumor Size, T/C%
1	0	0.0
4	0	109.9
8	0	59.9
11	0	16.1
15	0	14.2
18	0	15.5
22	0	13.0
25	0	17.1

The results for each of the compositions on day 26 are set forth in table 2:

TABLE 2

Dose-response evaluation of Antitumor activity of NDGA on Day 26

Composition	NDGA Dose %	Tumor Wt. (grams)	Relative Tumor Size, T/C%
A	1.53	5121.0	112.0
B	2.49	5827.0	129.8
C	3.41	5071.5	110.3
D	4.61	3390.9	71.7
E	6.36	3249.4	70.5
F	7.62	2650.3	56.0
G	9.44	1650.1	32.7
H	15.40	955.5	16.8
I	18.40	942.0	17.1

Example 3

The antiproliferative effect of NDGA on CMT-12 cultured canine breast adenocarcinoma tumor cells was evaluated in clonogenic (cancer cell) assays.

Single cell suspensions of tumor cells harvested from cultured flasks were exposed to the different compositions of NDGA for one hour at 37° C in liquid medium, and the cells were then washed twice, suspended in agarose medium and plated and the number of colony forming cells were determined. Results are expressed as percent inhibition of survival of clonogenic cells in treated cultures relative to nontreated control cultures. Significant anticancer activity was defined as > 70% inhibition of the survival of colony-forming (tumor) cells.

The results of the clonogenic assay using CMT 12 canine mammary carcinoma cells are presented in Table 3.

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Table 3

Composition	No. Tumor Colonies Surviving	% Inhibition
5 MicroMolar NDGA	229.7 ± 10.9	0
10 MicroMolar NDGA	173.3 ± 23.3	82.5
18 microMolar NDGA	190 ± 16.3	90.9
27 microMolar NDGA	40 ± 16.3	98.1
56 microMolar NDGA	3.3 ± 4.7	99.8

Example 4

Compositions of NDGA were tested for their ability to inhibit in vitro growth of the MC-1 equine sarcoid-derived cell line, in experiments similar to those of Example 3.

Compositions containing NDGA were uniformly successful in inhibiting colony growth over the duration of the assay, an effect which was especially noticable at concentrations of 27 and 56 microMolar NDGA.

Table 4

Percentage Inhibition of Colony Growth At Day 14

Amount NDGA (MicroMolar)	Experiment and % Inhibition			% Inhibition (Mean)
	#1	#2	#3	
18	20.9	36.7	39.5	32.4
27	32.8	58.9	49.3	47.0
56	33	62.2	40.7	45.3

EXAMPLE 5

The antitumor effect of NDGA against the human lung tumor cell line LX-T was determined utilizing a clonogenic assay.

The human lung tumor cell line, LX-T, which was derived from the solid tumor, LX-1, was cultured in the standard medium RPMI-1640 + 10% fetal calf serum (FCS). A stock solution (10^{-2}M) of NDGA was prepared by dissolving 32.04 mg of NDGA in 4 ml DMSO and 6 ml distilled H_2O. Serial dilutions of the test stock solutions were made in 15 ml of Ca^{2+} - and Mg^{2+}-free Hank's balanced salt solution (HBSS).

The LX-T cells were incubated in the presence of various amounts of NDGA, and the antitumor effect was determined by measuring the DNA control of the LX-T nuclei using DNA flow cytometric analysis with a DNA-specific fluorochrome, 4',6-diamidino-2-phenylindole (DAPI).

Table 5A shows the effective doses at different responses (ED_x) where x represents 50, 75, 90 or 95% cell growth inhibition.

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TABLE 5A

Calculated ED_x for NDGA (MicroMolar ±SD)

ED(50)	17.6 ± 4.07
ED(75)	26.6 ± 12.11
ED(90)	41.1 ± 28.10
ED(95)	55.9 ± 46.79

For comparison, Table 5B lists the $ED_{(50)}$ for three known anticancer drugs along with the $ED_{(50)}$ for NDGA.

TABLE 5B

Drug Name	ED(50) microMolar
5-FU	102.23
Adriamycin	25.6
Mutamycin	18.43
NDGA	17.6

EXAMPLE 6

The in vivo antitumor effect of NDGA at various survival levels was determined using MX-1 (human breast adenocarcinoma) cells implanted subcutaneously in the flank of nude mice.

Tumors which reached the 25-100 mm^2 range were used for the experiment. 0.1 ml of the test compound in solution was injected directly into the tumor. The tumors were measured periodically to determine their weight until 60 days after the initial treatment or all mice had died. Mice which showed no evidence of tumors were kept for 60 days to evaluate potential for tumor recurrence, at which time tumor characteristics, if any, were recorded.

The effective doses (ED_x) of NDGA at different response levels are provided in Table 6.

TABLE 6

ED_x (micromoles) for NDGA

Response Level	Micromoles
ED(50)	13.62
ED(75)	25.66
ED(90)	48.33
ED(95)	74.34

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EXAMPLE 7

A composition containing 17.6% NDGA and 1% BHT in Pego 400 was tested for antineoplastic activity in athymic mice implanted within human breast adenocarcinoma, MX-1. Each animal was innoculated intradermally on the dorsum near the nape of the neck with 0.5 ml of a MX-1 homogenate. The animals were treated by topical application with the NDGA compositions after day 23. The results were given in Table 7.

TABLE 7

Test Compostion	Tumor Free 60 Days	Tumor Re-currence
17.6% NDGA/1% BHT in PEGO 400	3/5	0

EXAMPLE 8

Compositions containing 4.4 wt/wt% of meso and DL NDGA were tested for efficacy against the MX-1 tumor as in Example 7.

The results are set forth in Table 8.

TABLE 8

Organic Compound	Tumor Free 60 Days	Tumor Re-currence
NDGA	4/5	0
dl-NDGA	4/5	0

EXAMPLE 9

Mice were exposed to dimethyl benzanthracene (DMBA), a classical tumor inducer, and to phorbol ester (TPA), a classical tumor promoter, after having been treated with NDGA.

Twenty mice were included in each of the following groups:

1. Positive control group: DMBA + TPA. Female SENCAR mice 6-8 weeks old received a single topical application of 10 mg of DMBA in 0.2 ml of acetone as the initiating agent. After one week, animals received twice weekly applications of tumor promoter TPA in 0.1 ml of acetone. Tumor formation was recorded weekly.

2. Antipromoting activity: DMBA + NDGA + TPA. 30 minutes prior to each application of TPA animals received topical application of NDGA (9 mg.) in 0.2 ml of acetone.

3. Anticarcinogenic activity: NDGA + DMBA + TPA. For five consecutive days animals received topical applications of NDGA (3 mg.) in 0.2 ml o acetone. 24 hours after the last treatment with NDGA, animals received DMBA and TPA exactly as in the positive control group.

NDGA was shown to nearly completely prevent TPA tumor promotion and to significantly reduce the potential of tumor induction by DMBA.

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EXAMPLE 10

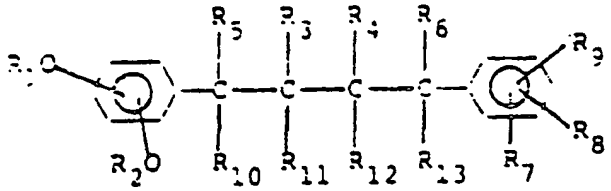
The ability of NDGA to absorb harmful sunlight radiation was tested.

A solution of NDGA in methanol was demonstrated to absorb strongly at 2816 Angstroms in the ultraviolet region, a sunlight wavelength known to result in sunburn.

Although the foregoing invention has been described in some detail by way of illustration and example for purposes of clarity and understanding, it will be obvious that certain changes and modifications may be practiced within the scope of the invention, as limited only by the scope of the appended claims.

Claims

1. A pharmaceutical composition characterized by comprising at least one catecholic butane of the formula:



wherein R_1 and R_2 are each independently H, lower alkyl, lower acyl, or alkylene;

R_3, R_4, R_5, R_6, R_{10}, R_{11}, R_{12} and R_{13} are each independently H or lower alkyl;

R_7, R_8 and R_9 are each independently H, hydroxy, lower alkoxy, lower acyloxy, or any two adjacent groups together may be alkylene dioxy.

2. A pharmaceutical composition as claimed in claim 1 characterised in that said at least one catecholic butane comprises nordihydroguaiaretic acid.

3. A pharmaceutical composition as claimed in claim 1 characterized in that said at least one catecholic butane comprises at least one lower alkyl ether derivative moiety.

4. A pharmaceutical composition as claimed in claim 1 or claim 3 characterised in that said at least one catecholic butane comprises at least one lower acyl ester derivative moiety.

5. A pharmaceutical composition as claimed in any one of claims 1, 3 or 4 characterised in that lower alkyl is C_1-C_6 alkyl, R_3 and R_4 are C_1-C_3 alkyl and lower acyl is C_1-C_6 acyl.

6. A pharmaceutical composition as claimed in claim 1 characterised in that said at least one catecholic butane is selected from 1,4-bis(3,4-dihydroxphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dihydroxyphenyl) butane; 1,4-bis(3,4-dimethoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-diethoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipropoxyphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl)-4-(3,4,5-trihydroxyphenyl) butane; 1,4-bis(3,4-diacetoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipropionyloxyphenyl)-2,3-dimethylbutane; 1,4-bis-(3,4-dibutyroyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-divaleroyloxyphenyl-2,3-dimethylbutane; 1,4-bis-(3,4-dipivaloyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dineopentylcarboxylphenyl)-2,3-dimethylbutane; 1-(3,4-dihyroxyphenyl) -4-phenylbutane; 1-(3,4-dihydroxyphenyl)-4-(2,5-dihydroxyphenyl) butane, and mixtures of two or more of these.

7. A pharmaceutical composition as claimed in claim 1 characterised in that the composition comprises a compound selected from all optical configurations of nordihydroguaiaretic acid tetrapivalate and nordihydroguaiaretic acid tetrapropionate.

8. A pharmaceutical composition as claimed in any one of claims 1 to 7 characterised in that it comprises 0.05-20 wt % of said at least one catecholic butane.

9. A pharmaceutical composition as claimed in any one of claims 1 to 7 characterised in that it comprises 0.1-10 wt % of said at least one catecholic butane.

10. A pharmaceutical composition as claimed in any one of claims 1 to 9 characterised in that it includes a pharmaceutically acceptable dilvent or carrier.

11. An injectable pharmaceutical composition characterised by comprising as an active ingredient at least one catecholic butane as defined in any one of claims 1 to 7.

12. A pharmaceutical composition for topical adminstration characterised by comprising as an active ingredient at least one catecholic butane as defined in any one of claims 1 to 7.

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13. A pharmaceutical composition as claimed in claim 12 characterised in that it is provided in the form of a lotion, cream, gel or ointment.

14. A sunscreening composition characterised by comprising at least one catecholic butane as defined in any one of claims 1 to 7.

15. A catecholic butane as defined in any one of claims 1 to 7 for use in the preparation of a medicament for the prevention of the occurance of or for the treatment of solid mammalian neoplasms.

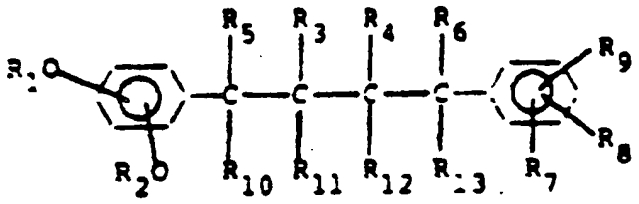
16. A catecholic butane as defined in any one of claims 1 to 7 for use in the preparation of a medicament for the prevention of the occurance of or for the treatment of disorders of the skin.

17. A method of improving the appearance of the skin of a mammal with acne which comprises administering to the skin of the mammal at the site of the acne a cosmetic composition comprising at least one catecholic butane as defined in any one of claims 1 to 7.

18. A method of preventing the appearance of the skin of a mammal which is to be exposed to sunlight from being disfigured by sunburn which comprises applying to the skin a sunscrrening composition comprising at least one catecholic butane as defined in any one of claims 1 to 7.

Claims for the following Contracting States : ES, GR

1. A process for preparing a pharmaceutical composition characterized by compounding a pharmaceutically acceptable diluent or carrier with at least one catecholic butane of the formula:



wherein R_1 and R_2 are each independently H, lower alkyl, lower acyl, or alkylene;

R_3, R_4, R_5, R_6, R_{10}, R_{11}, R_{12} and R_{13} are each independently H or lower alkyl;

R_7, R_8 and R_9 are each independently H, hydroxy, lower alkoxy, lower acyloxy, or any two adjacent groups together may be alkylene dioxy.

2. A process as claimed in claim 1 characterised in that said at least one catecholic butane comprises nordihydroguaiaretic acid.

3. A process as claimed in claim 1 characterized in that said at least one catecholic butane comprises at least one lower alkyl ether derivative moiety.

4. A process as claimed in claim 1 or claim 3 characterised in that said at least one catecholic butane comprises at least one lower acyl ester derivative moiety.

5. A process as claimed in any one of claims 1, 3 or 4 characterised in that lower alkyl is C_1-C_6 alkyl, R_3 and R_4 are C_1-C_3 alkyl and lower acyl is C_1-C_6 acyl.

6. A process as claimed in claim 1 characterised in that said at least one catecholic butane is selected from
1,4-bis(3,4-dihydroxphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dihydroxyphenyl) butane; 1,4-bis(3,4-dimethoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-diethoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipropoxyphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl)-4-(3,4,5-trihydroxyphenyl) butane; 1,4-bis(3,4-diacetoxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dipropionyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dibutyroyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-divaleroyloxyphenyl-2,3-dimethylbutane; 1,4-bis(3,4-dipivaloyloxyphenyl)-2,3-dimethylbutane; 1,4-bis(3,4-dineopentylcarboxylphenyl)-2,3-dimethylbutane; 1-(3,4-dihydroxyphenyl) -4-phenylbutane; 1-(3,4-dihydroxyphenyl)-4-(2,5-dihydroxyphenyl) butane, and mixtures of two or more of these.

7. A process as claimed in claim 1 characterised in that the composition comprises a compound selected from all optical configurations of nordihydroguaiaretic acid tetrapivalate and nordihydroguaiaretic acid tetrapropionate.

8. A process as claimed in any one of claims 1 to 7 characterised in that it comprises 0.05-20 wt % of said at least one catecholic butane.

9. A process as claimed in any one of claims 1 to 7 characterised in that it comprises 0.1-10 wt % of said at least one catecholic butane.

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10. A method of improving the appearance of the skin of a mammal with acne which comprises administering to the skin of the mammal at the site of the acne a cosmetic composition comprising at least one catecholic butane as defined in any one of claims 1 to 7.

11. A method of preventing the appearance of the skin of a mammal which is to be exposed to sunlight from being disfigured by sunburn which comprises applying to the skin a sunscrrening composition comprising at least one catecholic butane as defined in any one of claims 1 to 7.

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